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The effects of cell compressibility, motility and contact inhibition on the growth of tumor cell clusters using the Cellular Potts Model

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HIGHLIGHTS

- We study the interplay between cell motility and compressibility within the Cellular Potts Model.
- At equal compression, clusters of motile cells grow faster than clusters of less motile cells.
- Contact inhibition compounds the effects of motility on cluster growth.
- Cells that experience significant compression have reduced growth rates.
- Our model produces cell size distributions observed in neuroblastoma clusters.

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ABSTRACT

There are numerous biological examples where genes associated with migratory ability of cells also confer the cells with an increased fitness even though these genes may not have any known effect on the cell mitosis rates. Here, we provide insight into these observations by analyzing the effects of cell migration, compression, and contact inhibition on the growth of tumor cell clusters using the Cellular Potts Model (CPM) in a monolayer geometry. This is a follow-up of a previous study (Thalhauser et al. 2010) in which a Moran-type model was used to study the interaction of cell proliferation, migratory potential and death on the emergence of invasive phenotypes. Here, we extend the study to include the effects of cell size and shape. In particular, we investigate the interplay between cell motility and compressibility within the CPM and find that the CPM predicts that increased cell motility leads to smaller cells. This is an artifact in the CPM. An analysis of the CPM reveals an explicit inverse-relationship between the cell stiffness and motility parameters. We use this relationship to compensate for motility-induced changes in cell size in the CPM so that in the corrected CPM, cell size is independent of the cell motility. We find that subject to comparable levels of compression, clusters of motile cells grow faster than clusters of less motile cells, in qualitative agreement with biological observations and our previous study. Increasing compression tends to reduce growth rates. Contact inhibition penalizes clumped cells by halting their growth and gives motile cells an even greater advantage. Finally, our model predicts cell size distributions that are consistent with those observed in clusters of neuroblastoma cells cultured in low and high density conditions.

1. Introduction

Tumorigenesis is a complex process in which cells acquire phenotypes that give them a competitive advantage (e.g., increased fitness) over untransformed cells. Most notably, these phenotypes include unrestricted proliferation and invasive potential, among other cancer hallmarks (Hanahan and Weinberg, 2011). Tumor cells may acquire a high proliferation potential through alterations in the growth signaling pathway. For instance, mutations which permanently activate the growth-regulating Ras gene are found in about 20% of all human tumors (Downward, 2003). A loss of function of the tumor suppressor gene p53, which is responsible for repairing DNA, regulating the cell cycle, and activating apoptosis, is also implicated in many tumors (Lehmann and Pietenpol, 2012). Such genetic mutations afford tumor cells a competitive advantage over surrounding tissues.

At the same time, genes associated with the migratory ability of cells have been found to increase cell fitness even though these genes do not directly affect cell mitosis rates. For example, while

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the cytoskeletal effector RhoC is not an oncogene (since RhoC does not transform normal cells), RhoC does influence cell migration and tumorigenicity (Clark et al., 2000; Stoletov et al., 2007). Similarly, overexpression of the cytoskeletal adaptor molecule ABI-1 in breast cancer cell lines enhances cell migration and invasion potential (Larkins et al., 2006), as does the integrin-associated focal adhesion kinase (Lim et al., 2008; Brunton et al., 2008).

We wish to understand what combinations of phenotypes give tumor cells enhanced fitness over untransformed cells. In this study, we focus on the individual and combined effects of cell motility, compression, and contact inhibition on tumor growth. In general, cells may move randomly, may move up gradients of chemical fields (chemotaxis), and may migrate along adhesion gradients (haptotaxis). At the sub-cellular level, polymerization and depolymerization of actin-derived cytoskeletal structures are most responsible for facilitating movement (Ananthakrishnan and Ehrlicher, 2007). Compressive stress, resulting from proliferation of clusters of tumor cells in a confined geometry, may induce cytoskeletal modifications and the emergence of invasive phenotypes (Tse et al., 2012; Ronan et al., 2012; Boghaert et al., 2012). Motile tumor cells, which are thought to be precursors of metastatic activity (Friedl and Wolf, 2003), tend to be difficult to image and detect and are also more difficult to treat.

We also investigate contact inhibition, a phenomenon that restricts cell proliferation and motility of cells that are in contact with other cells (Abercrombie, 1979). The process of contact inhibition is well understood. Adherins junctions, or interactions between cells via receptors, play a significant role in signaling a cell to stop growth and movement. The transmembrane receptors nectins, cadherins, integrins and growth factor receptors have all been implicated in the signaling pathway of contact inhibition (St. Croix et al., 1998; Takai et al., 2008). A distinctive characteristic of cancer cells is partial or complete insensitivity to contact inhibition (Friedl and Brocker, 2000; Miekus et al., 2005) although some immortalized cancer cell lines remain sensitive to contact inhibition (e.g., neuroblastoma, Brodie et al., 1993). In this work, we explore how responsiveness to contact inhibition affects cluster growth and demonstrate the competitive advantage a loss of contact inhibition affords to tumor clusters.

To investigate the tumor behavior, we use a mathematical/computational model. Tumor models can be organized into three broad categories describing simulation dynamics: discrete, continuous, and hybrid. Each type has their benefits and drawbacks, with increased biological detail being associated with increased computational cost. See for example the reviews (Anderson and Quaranta, 2008; Byrne, 2010; Cristini and Lowengrub, 2010; Lowengrub et al., 2010; Rejniak and Anderson, 2011; Frieboes et al., 2011). Discrete simulations most easily incorporate biological laws and model cellular interactions, but this level of detail demands substantial computational power. Continuous models are useful for simulating the growth dynamics at larger (tissue) scales, but are not able to distinguish among individual cells. Hybrid models (Bearer et al., 2009; Stolarska et al., 2009; Frieboes et al., 2010; Cristini and Lowengrub, 2010; Kim and Othmer, 2013), which combine features of both discrete and continuous models, are a promising approach but require more development before they can be broadly used.

In a recent study, Thalhauser et al. (2010) investigated the interactions of proliferation, migratory potential and cell death on the emergence of invasive phenotypes using spatial generalizations of the discrete, stochastic Moran process where the size and shape of the cells is not considered. In this study, migration is found to have a direct positive impact on the ability of a single mutant cell to invade a pre-existing colony and that a decrease in the proliferation potential can be compensated by an increase in the potential for cells to move. Here, we extend the study to include the effects of cell size and shape and cell–cell interactions such as adhesion and contact inhibition.

In this work, we focus on the growth of small cell clusters and we use the Glazier-Graner Hogeweg model (GGH), a discrete lattice-based modeling environment (Glazier and Graner, 1993; Izaguirre et al., 2004; Cickovski et al., 2007; Chentetal, 2007; Swat et al., 2012; Scianna et al., 2013). This model, also known as the Cellular Potts Model (CPM), is very versatile and has been used to model, for example, gastrulation (Longo et al., 2003; Vlaslev et al., 2010), angiogenesis (Peirce et al., 2004; Ambrosi et al., 2005; Merks et al., 2006; Shirinifard et al., 2009), cell sorting (Zhang et al., 2011), somite formation (Hester et al., 2011), intracellular dynamics (Andasari et al., 2012), vasculogenesis (Merks and Glazier, 2006; Scianna et al., 2011) and tumor growth (Dormann and Deutsch, 2002; Turner and Sherratt, 2002; Ghaemi and Shahrokhi, 2006; Bauer et al., 2007; Rubenstein and Kaufman, 2008; Andasari et al., 2012). Continuum limits of the CPM have also been analyzed in the context of cell chemotaxis and solutions are well-described by Fokker–Planck equations for the cell probability density function (Alber et al., 2007, 2006). Very recently, the CPM has been extended to simulate individual cells migrating in fibrous extracellular matrix (Scianna and Preziosi, 2013a, 2013b). Further, as part of a recent study of cell differentiation and migration, a thermodynamic analysis of the CPM was performed (Harrison et al., 2011). In Voss (2012), an analysis of the CPM at multiple time scales was conducted.

Through our investigation, we find that there is an interplay between cell motility and compressibility within the CPM. Interplay between cell characteristics and interactions has previously been noted as an important aspect of the CPM that requires further study (Voss, 2012). In particular, the CPM predicts that increased cell motility leads to smaller cells. In fact, for sufficiently large cell motilities, cells may become unstable and actually vanish. This is an artifact in the CPM and we are not aware of any correlations between cell size and cell motility being observed experimentally. An analysis of the CPM enables us to derive an inverse-relationship between the cell stiffness and motility parameters that we use to compensate for motility-induced changes in cell size in the CPM so that in the corrected CPM, cell size is independent of the cell motility.

The remainder of the paper is organized as follows. In Section 2, we present the CPM model. In Section 3, results are presented and analyzed. Finally, in Section 4, we draw conclusions and discuss further work.

2. The model

2.1. The cellular potts model

The CPM utilizes generalized cells mapped out on a uniform 2D-Cartesian grid. These generalized cells are specially extended objects composed of a collection of grid cells (sometimes referred to as pixels) and can include both cells and extra-cellular matrix (referred to as "medium"). Each generalized cell is assigned an index, σ, and has cell type $\tau(\sigma)$. Here, we use two different generalized cell types: $\tau = 1$ (medium or ECM) and 2 (cell).

The simulation is stochastic and proceeds via a Monte Carlo method by repeating a basic operation, called an index-copy attempt. A grid cell, $\vec{i}$, is chosen at random from the simulation grid and attempts to copy its index $\sigma(\vec{i})$ onto a neighboring grid cell, $\vec{i}_{\text{neighbor}}$. The simulation accepts this index-copy attempt with probability given by the Boltzmann acceptance function:

$$P(copy) = \begin{cases} 1 & \Delta H \le 0, \\ e^{-\Delta H/T_m} & \Delta H > 0. \end{cases}$$